INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE

ZENTRUM FÜR ANGEBORENE HERZFEHLER

Universitätsklinik für Kardiologie
Klinikdirektor
Prof.Dr.med. Stephan Windecker

Effect of phosphodiesterase-5 inhibition with Tadalafil on SystEmic Right VEntricular size and function – a multi-center, double-blind, randomized, placebo-controlled clinical trial – SERVE Trial

Clinical Study Protocol

Study Type:	Clinical trial with Investigational Medicinal Product (IMP)
Study Categorisation:	Clinical Trial of Medicinal Product, Risk category B
Study Registration:	www.clinicaltrials.gov, Swiss National Clinical Trials Portal (SNCTP)
Study Identifier:	SNF Project 33IC30_166855
Sponsor	Inselspital, Cardiology, Bern University Hospital, 3010 Bern
Coordinating Investigator:	Prof. Dr. Markus Schwerzmann
Investigational Product:	Tadalafil
Protocol Version and Date:	Version 1 / 12.10.2016

The Sponsor / Coordinating Investigator has approved the current version of the protocol version and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor / Coordinating Investigator: Prof. Dr. Markus Schwerzmann

Place/Date	Signature

Local Principal Investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site:

Principal investigator:

Place/Date	Signature

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STUDY SYNOPSIS

Sponsor:	Inselspital, Bern University Hospital, 3010 Bern
Coordinating – Investigator:	Prof. Dr. Markus Schwerzmann
Study Title:	Effect of phosphodiesterase-5 inhibition with Tadalafil on systemic right ventricular size and function – a multi-center, double-blind, randomized, placebo-controlled clinical trial
Short Title / Study ID:	SERVE
Protocol Version and Date:	Version 1 / 12.10.2016
Trial registration:	www.clinicaltrials.gov, SNCTP
Study category and Rationale:	Clinical trials of medicinal products, category B: the medicinal product is authorized in Switzerland but will be used in an indication different to that in the prescribing information.
Clinical Phase:	Clinical study phase 3
Background and Rationale:	Currently, there are an estimated 300-600 adults living in Switzerland with congenital heart disease (CHD) and a right ventricle (RV) in subaortic (systemic) position. This includes adults with prior atrial switch operations for complete transposition of the great arteries (D-TGA) and adults with congenitally corrected transposition of the great arteries (ccTGA). Although midterm survival is favourable, late outcome is compromised by ventricular dysfunction of the systemic RV, end-stage heart failure, and premature death. Medical heart failure therapy (ACE-inhibitors, beta-blockers, aldosterone antagonists) has been shown to improve ventricular function and survival in patients with left heart failure from acquired heart disease. Unfortunately, case-reports and studies failed to show similar clinical benefits of these drugs in adults with a failing systemic RV. Currently, the only established end-stage therapy for a failing systemic RV is heart transplantation. Given the ubiquitous shortage of donor organs and the number of adults at risk, medical options to improve the fate of patients with a systemic RV are urgently needed. The RV and left ventricle (LV) have different embryological origins, myocardial architecture and contractile properties. In response to increased afterload, as in an RV in systemic position, the RV expresses a fetal gene pattern, with an increase in phosphodiesterase (PDE)-5 expression. PDE-5 is not expressed in the normal RV, but is up-regulated in the hypertrophied RV. PDE-5 inhibition increases contractility in experimental models of RV hypertrophy, but not in the normal RV. In clinical practice, the effects of PDE-5 inhibition on systemic RV function and exercise capacity in adults with TGA have not been tested.
Objective(s):	This study assesses in a double-blind, randomized, placebo-controlled multi-center pilot trial the effect of PDE-5 inhibition with Tadalafil on RV size and function, exercise capacity and neurohumoral activation in adults with a systemic RV over a 3-year follow-up period.

Outcome(s):	Primary endpoint: Change in mean end-systolic RV volumes (RV ESV) from baseline to study end at 3 years of follow-up, measured by cardiovascular magnetic resonance imaging (CMR) or cardiac multirow detector computed tomography (CMDCT) in patients with contraindications for CMR, or at the time of permanent discontinuation of the randomized treatment if stopped before 3 years of follow-up. Secondary endpoints: Change in mean systemic RV ejection fraction (RV EF) from baseline to study end at 3 years of follow-up, measured by CMR or CMDCT in patients with contraindications for CMR, or at the time of permanent discontinuation of the randomized treatment if stopped before 3 years of follow-up. Change in exercise capacity measured as peak VO_2 during cardiopulmonary exercise testing and change in serum neurohormonal activation from baseline to study end at 3 years of follow-up, or at the time of permanent discontinuation of the randomized treatment if stopped before 3 years of follow-up.
Study design:	Double-blind, randomized placebo controlled multicenter superiority study.
Inclusion / Exclusion criteria:	Inclusion criteria: Adults (≥18 years) with a systemic RV due to D-TGA repaired with an atrial switch procedure or due to ccTGA. Exclusion criteria: No informed consent; myocardial infarction, stroke, or open heart surgery in the previous 3 months; expected heart transplant within the next 6 months; pregnant or nursing women; severe renal insufficiency; hypersensitivity to Tadalafil; known allergy to iodinated or Gadolinium-based contrast agents.
Measurements and procedures:	Baseline visit: Quality of life (QoL), clinical exam, ECG, holter ECG, echocardiography, CMR/CMDCT, CPET, routine blood work, neurohormones Visit 1 (4 week follow-up): Clinical exam, bloodwork Visit 2 (1 year follow-up): QoL, clinical exam, ECG, echocardiography, CMR/CMDCT, routine blood work, neurohormones Visit 3 (2 year follow-up): Clinical exam, ECG, echocardiography, routine blood work Visit 4 (3 year follow-up): QoL, clinical exam, ECG, holter ECG, echocardiography, CMR/CMDCT, CPET, routine blood work, neurohormones
Study Product / Intervention:	Tadalafil 20 mg p.o. OD for 3 years vs. placebo p.o. OD (the study medication will be provided by the pharmacy of the University Hospital Bern). All participants will be started on Tadalafil 20 mg or placebo OD without any titration period.
Number of Participants with Rationale:	Sample size calculation is based on the change in RV ESV. 98 patients need to be included (49 patients for each group), allowing a dropout rate of 20%

Study Duration:	June 2016 – May 2021, e.g. 5 years
Study Extension:	No extension is foreseen. After end of the study treatment period subjects will receive standard-of-care treatment as deemed necessary by the treating physician.
Study Schedule:	Month Year of First-Participant-In: 06/2017 Month Year of Last-Participant-Out: 05/2021
Investigator(s):	Coordinating Investigator: Prof. Dr. Markus Schwerzmann, Zentrum für angeborene Herzfehler, Kardiologie, Universitätsspital Inselspital, 3010 Bern; markus.schwerzmann@insel.ch; +41 (0) 31 632 78 59 Members of the Steering Committee and Co-Principal Investigators: Dr. Judith Bouchardy, Service de Cardiologie, CHUV, 1000 Lausanne and HUG, 1200 Genève PD Dr. Matthias Greutmann, Leiter Angeborene Herzfehler, Universitäres Herzzentrum, UniversitätsSpital Zürich, 8000 Zürich PD Dr. Daniel Tobler, Leiter Angeborene Herzfehler, Kardiologie, Universitätsspital Basel, 4031 Basel Co-Investigators: Dr. Reto Engel, Kardiologie, Kantonsspital St. Gallen, 9000 St. Gallen Prof. Dr. H. Gabriel, Ambulanz für angeborene Herzfehler im Erwachsenenalter, Universitätsklinik für Innere Medizin II, Medizinische Universität Wien, A
Study Centre(s):	Multicentric study in Switzerland and Austria, with 7 centers: - University Hospital Basel - University Hospital Bern (Inselspital) - University Hospital Geneva (HUG) - University Hospital Lausanne (CHUV) - University Hospital Zurich (USZ) - Kantonsspital St. Gallen - University Hospital Vienna
Statistical Considerations:	Sample size calculation is based on the change in mean RV ESV. In a representative sample of n=79 TGA patients with a systemic RV from Bern and Zurich with CMR data, the mean RV ESV was 122±34 ml. Assuming that mean RV ESV improves or remains stable in the Tadalafil group and increases in the Placebo group by 20% to 146±39 ml, 78 patients are required to obtain an 80% power with a two-sided alpha set at 0.05 to detect a 20% change in volumes between the 2 treatment groups. Considering a possible dropout of 20%, 98 patients will be required (49 patients for each group).
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

ABBREVIATIONS

ACE-I	Angiotensin-Converting-Enzyme inhibitor
AE	Adverse Event
ARB	Angiotensin II Receptor Blocker
BNP	Brain Natriuretic Peptide
CA	Competent Authority (e.g. Swissmedic)
cGMP	cyclic Guanosine Mono-Phosphate
ccTGA	congenitally corrected Transposition of Great Arteries
CEC	Competent Ethics Committee
CHD	Congenital Heart Disease
ClinO	Ordinance on Clinical Trials in Human Research 810.305[1]
CMDCT	Cardiac Multirow Detector Computed Tomography
CMR	Cardiac Magnetic Resonance imaging
CPET	CardioPulmonary Exercise Testing
(e)CRF	(electronic) Case Report Form
CRIB	Cardiovascular Research Institute Basel
CYP	human CYtochromes P450
DSMB	Data Safety Monitoring Board
D-TGA	Complete Transposition of Great Arteries
ECG	ElectroCardioGram
EF	Ejection Fraction
EOT	End Of Treatment
ESV	End-Systolic Volume
GCP	Good Clinical Practice
GUCH	Grown-Up Congenital Heart disease
HF	Heart Failure
HRA	Federal Act on Research involving Human Beings 810.30[2]
Hs-cTn	High sensitive cardiac Troponin
IB	Investigator's Brochure
ICH	International Conference on Harmonzation
IMP	Investigational Medicinal Product
IIT	Investigator-Initiated Trial

[1] Verordnung über klinische Versuche in der Humanforschung (Verordnung über klinische Versuche, KlinV) vom 20. September 2013 / Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain (Ordonnance sur les essais cliniques, OClin) du 20 septembre 2013.

[2] Humanforschungsgesetz, HFG Bundesgesetz über die Forschung am Menschen (Bundesgesetz über die Forschung am Menschen, HFG) vom 30. September 2011/ Loi fédérale relative à la recherche sur l'être humain (loi relative à la recherche sur l'être humain, LRH) du 30 septembre 2011.

LV	Left Ventricle
MR-proADM	Mid-Regional pro-ADrenoMedullin
MR-proANP	Mid-Regional pro-Atrial Natriuretic Peptide
Nt-proBNP	N-terminal pro-Brain Natriuretic Peptide
OD	Once per Day
PAH	Pulmonary Arterial Hypertension
PDE	Phospho-Di-Esterase
PI	Principal Investigator
QoL	Quality of Life
RV	Right Ventricle
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNCTP	Swiss National Clinical Trials Portal
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Transposition of Great Arteries
TID	Ter In Die
TMF	Trial Master File

STUDY SCHEDULE

Visit	BL*	Visit 1	PC1**	PC2**	PC3**	Visit 2	PC4**	Visit 3	PC5**	Visit 4	PC 6 Safety FU
Time (months)	0	1	3	6	9	12	18	24	30	36	37
Window (weeks)	0	+ 2	+2	+2	+2	+ 4	+2	+ 4	+2	+ 4	± 1
Informed Consent	X										
Eligibility criteria	X										
Demography	X										
Medical history	X										
QoL	X					X				X	
Randomization	X										
Clinical examination	X	X				X		X		X	
IMP delivery	X					X		X			
IMP accountability		X				X		X		X	
ECG	(X)	X				(X)		(X)		(X)	
Holter	(X)									(X)	
CMR / CMDCT	X					X				X	
CPET	X									(X)	
Blood analysis	(X)	X				(X)		(X)		(X)	
Neurohormones	X					X				X	
TTE	(X)					(X)		(X)		(X)	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	
Adherence			X	X	X		X		X		
AE/SAE		X	X	X	X	X	X	X	X	X	X

(X) Not study specific, only collected if performed per routine

* Baseline (BL) exams

**Phone call (PC) to control adherence to IMP

1. STUDY ADMINISTRATIVE STRUCTURE

Sponsor:

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Pharmacy:

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Device Safety Monitoring Board:

An independent Data Safety Monitoring Board (DSMB) will be commissioned for this study. This committee will consist of two cardiologists, independent from the study. The DSMB will monitor the progress of the study and ensure that the safety of subjects is not compromised. Any recommendations from the DSMB will be made available to the Sponsor / Coordinating Investigator.

2. ETHICAL AND REGULATORY ASPECTS

The decision of the competent ethics committee (CEC) and Swissmedic concerning the conduct of the study will be made in writing to the Sponsor / Coordinating Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities will be implemented.

2.1 Study registration

The study has been registered under www.clinicaltrials.gov as well as in the Swiss National Clinical Trials Portal (SNCTP - KOFAM).

2.2 Categorisation of study

This is a clinical trial of medicinal products category B, as the medicinal product is authorized in Switzerland but will be used in an indication different to that in the prescribing information.

2.3 Ethical conduct of the study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH[3], the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.4 Declaration of interest

The study is financially supported by an SNF grant (SNF grant number 33IC30_166855). There is no funding from industry and none of the applicants has any conflict of interest with respect to the company selling Tadalafil or the placebo for the study purposes.

2.5 Patient information and informed consent

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant will be informed that his/her medical records may be examined by authorized individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Enough time (at least 48 hours) will be given to the participant to decide whether to participate or not.

The patient information sheet and the consent form will be submitted to the CEC and to the competent

[3] Declaration of Helsinki, Version October 2013 / International Conference on Harmonization (ICH, 1996) E6 Guideline for Good Clinical Practice / International Conference on Harmonization (ICH, 1997) E8 Guideline: General Considerations for Clinical Trials

authority (CA; as applicable) to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

2.6 Participant privacy and confidentiality

The investigators affirm and uphold the principles of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers corresponding to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor, a CA (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.7 Early termination of the study

The Sponsor / Coordinating Investigator may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns;
- insufficient participant recruitment;
- when the safety of the participants is doubtful or at risk, respectively;
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise;
- early evidence of harm of the experimental intervention.

The DSMB will have the responsibility for recommending early termination of the study to the Sponsor / Coordinating Investigator, which will have ultimate authority/responsibility for making the decision. The criteria that the DSMB will follow to determine whether/when to recommend termination of the study will be based on:

- the analysis of adverse events (AE) / serious adverse events (SAE);
- results of parallel clinical studies;
- results of parallel animal studies (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).

2.8 Protocol amendments

Substantial amendments are only implemented after approval of the CEC and CA respectively.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor / Coordinating Investigator and the CEC/CA. Such deviations shall be documented and reported to the Sponsor / Coordinating Investigator and the CEC/CA as soon as possible.

All non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and rationale

The number of adults with congenital heart disease (CHD) continues to increase.[1, 2] Residual lesions and sequelae of previous interventions predispose to higher morbidity and mortality rates.[3]

Currently, there are an estimated 300-600 adults living in Switzerland with CHD and a right ventricle (RV) in subaortic (systemic) position. These are adults with prior atrial switch operations (i.e. a Senning or Mustard procedure) for complete transposition of the great arteries (D-TGA; figure 1) or adults with congenitally corrected transposition of the great arteries (ccTGA; figure 2) and no switch procedure.[4] Although midterm survival is favorable, late outcome is compromised by ventricular dysfunction of the systemic RV, end-stage heart failure, and premature death.[5-9] In a recent longitudinal study of 91 consecutive D-TGA patients with an atrial switch procedure, cumulative survival after surgery was 77% after 30 years, and 68% after 39 years. RV systolic function (i.e. systemic ventricular function) was impaired in all but one patient at last follow-up, and 14% newly developed heart failure in the last decade of follow-up.[6] Systemic RV dysfunction usually precedes the onset of clinical heart failure in these patients, and once symptoms occur, they are a strong predictor of death.[7, 8, 10-13] By their mid-40s, also more than half of patients with ccTGA exhibit moderate-to-severe RV dysfunction and a similar proportion have clinical signs of heart failure.[9]

Figure 1: D-TGA

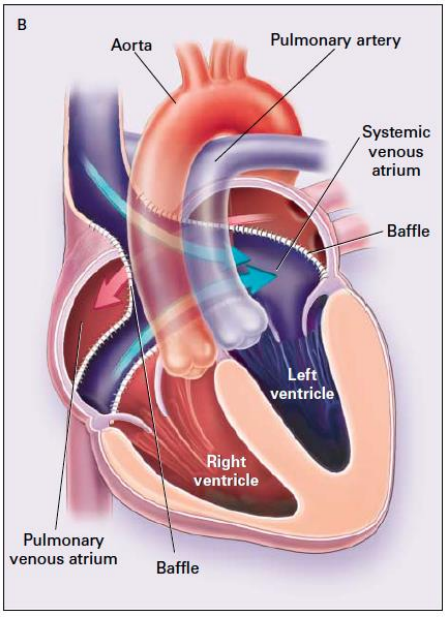
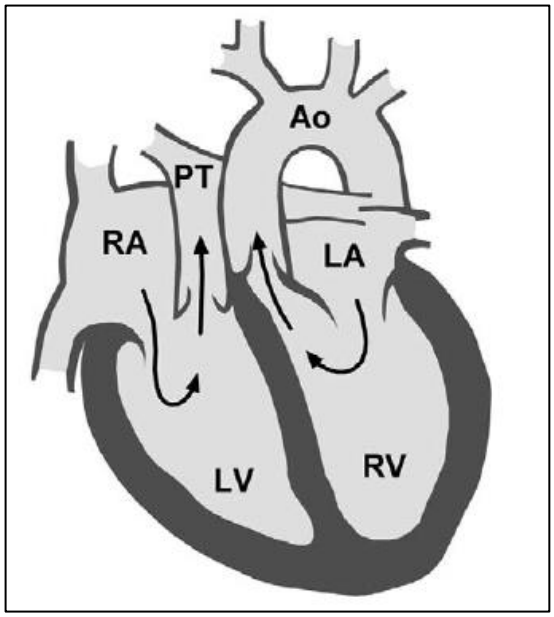


Figure 2: cc-TGA[4]



Medical heart failure therapy with angiotensin-converting-enzyme inhibitors (ACE-I), Angiotensin II receptor blockers (ARBs), beta-blockers, and aldosterone antagonists has been shown to improve ventricular function and survival in patients with left ventricular (LV) failure from acquired heart

[4] *Figure 1*: In D-TGA there is atrioventricular concordance and ventriculoarterial discordance. With the "atrial switch" operation, a pericardial baffle is created in the atria, so that blood returning from the systemic venous circulation is directed into the left ventricle (LV) and then to the pulmonary artery (blue arrows), whereas blood returning from the pulmonary venous circulation is directed into the RV and then to the aorta (red arrow). The RV remains the systemic ventricle (picture from 14.Brickner, M.E., L.D. Hillis, and R.A. Lange, *Congenital heart disease in adults. First of two parts.* N Engl J Med, 2000. **342**(4): p. 256-63.)

Figure 2: Schematic diagram of ccTGA in which there is both atrioventricular and ventriculoarterial discordance. Ao: aorta; LA: left atrium; LV: morphologic left ventricle; PT: pulmonary trunk; RA: right atrium; RV: morphologic right ventricle (picture from 10. Warnes, C.A., *Transposition of the great arteries.* Circulation, 2006. **114**(24): p. 2699-709.).

disease.[15] However, several studies failed to show a similar clinical benefits of these drugs in adults with a failing systemic RV[16]:

- ARBs showed no significant beneficial effect on systemic RV function, exercise capacity, neurohumoral activation or quality of life,[17-19] and neither the ACE-I Ramipril[20] nor Enalapril[21] had a positive effect on exercise performance or ventricular function.
- In two small and non-randomized trials, beta-blockers (Carvedilol or Metoprolol) resulted in an improvement in systolic RV function, but had no effect on exercise capacity.[22, 23] However, in the only randomized, double-blind and placebo-controlled trial using Carvedilol in children and adolescents with CHD and heart failure, beta-blocker therapy was of no benefit in those with a systemic RV.[24] In addition, adults with D-TGA and an atrial switch procedure a prone to bradyarrhythmias, an important limitation to the use of beta-blockers in this population.
- In an exploratory trial, the aldosterone antagonist Eplerenone had no effect on systemic RV function and exercise capacity after 1 year of therapy.[25]
- Cardiac resynchronization therapy has shown to improve acute hemodynamics in selected adults with a failing systemic RV.[26, 27] However, only a minority of patients with a systemic RV may be potentially eligible candidates, and data on long-term outcome are lacking.

Currently, the only established therapy for end-stage heart failure with a systemic RV is heart transplantation.[28] Ventricular assist devices can be used as bridge to transplant.[29] Given the ubiquitous shortage of donor organs and the number of adults at risk, medical options to improve the fate of a systemic RV are urgently needed. Considering the negative trials outlined above, one can argue that in the setting of a failing systemic RV the pursuance of therapies developed for treatment of LV failure has to be abandoned.[30] New approaches have to be investigated.

The RV and LV have different embryological origins, myocardial architecture and contractile properties.[31, 32] In response to increased afterload, as present in an RV in systemic position, the RV expresses a fetal gene pattern with an increase in phosphodiesterase-5 (PDE-5) expression.[33] PDE-5 is not expressed in the normal RV, but is up-regulated in hypertrophied RV myocardium. PDE-5 inhibitors increase contractility in experimental models of RV hypertrophy, but not in the normal RV.[33] PDE-5 inhibitors increase cyclic guanosine monophosphate (cGMP) levels, which under normal circumstances would activate protein kinase G, decrease intracellular calcium levels, and reduce contractility.[34] However, in hypertrophied myocardium, protein kinase G activity is inhibited, so cGMP preferentially shifts to its other pathway with inhibition of PDE-3. Thus, in hypertrophied RV myocardium, PDE-5 inhibitors increase cGMP — which inhibits PDE-3 — thereby increasing cyclic adenosine monophosphate (cAMP), which activates protein kinase A; this, in turn, increases intracellular calcium and contractility.[33]

To the best of our knowledge, the effects of PDE-5 inhibition on systemic RV function and exercise capacity have not yet been tested in adults with a systemic RV. No study is registered at clinicaltrials.gov or has been published so far.

3.2 Investigational treatment and indication

In pulmonary arterial hypertension (PAH) patients, Sildenafil and Tadalafil are the most widely used PDE-5 inhibitors. Tadalafil has a longer half-live (18 hours) than Sildenafil (3-4 hours) and higher selectivity for PDE-5.[35] Tadalafil can be taken as a single daily dose. In studies investigating the effects of Tadalafil on cardiac and circulatory function, single Tadalafil doses up to 50 mg have been reported to be safe in terms of an absence of significant systemic vasodilation.[35] In several large PAH trials, Tadalafil therapy was well tolerated through up to 68 weeks of dosing.[36, 37] In the large number of patients using PDE-5 inhibitors for treating erectile dysfunction, Tadalafil had an excellent safety profile without significant cardiovascular safety issues.[38] In over 30 trials, more than 12’000 men (mean age 55 years) with erectile dysfunction received Tadalafil and 2’000 men (mean age 56 years) received placebo. Tadalafil 2 mg to 50 mg was taken as needed, 3 times/week, or once a day (OD). Co-morbidities at baseline included hypertension (31%), diabetes (21%), hyperlipidemia (17%), and coronary artery disease (5%). Across all trials, the incidence rate of serious cardiovascular events

was similar in Tadalafil-treated men compared to placebo-treated ones, independent if Tadalafil was used as needed, 3 times/week, or OD.[39]

The human cytochromes P450 (CYPs) are the major family of enzymes involved in the oxidative metabolism of drugs. In this family of enzymes, CYP3A is the dominant CYP in terms of both expression levels in the liver and the number of drugs metabolized. Clinical studies demonstrated that the pharmacokinetics of 2 different CYP3A substrates, Midazolam and Lovastatin, were virtually unchanged after Tadalafil co-administration. Thus, therapeutic concentrations of Tadalafil do not produce clinically significant changes in the clearance of drugs metabolized by CYP3A.[40]

For all these reasons, we decided to use Tadalafil as PDE-5 inhibitor in this clinical study. In the PHIRST trial, a study with PAH patients, Tadalafil 2.5 mg, 10 mg, 20 mg and 40 mg OD was compared against placebo.[41] There was no significant difference between Tadalafil 20 mg OD vs. 40 mg OD with respect to the hemodynamic measures and changes in 6 minute walking distance. In the PHIRST-2 extension trial, patients receiving either 20 mg or 40 mg of Tadalafil, had both a sustained beneficial effect for up to 52 additional weeks of treatment.[37] The most common adverse effect of Tadalafil in this trial was headache, occurring in 14% of patients with the 20 mg dose and 28% of patients with the 40 mg dose.

Overall, 20 mg Tadalafil seems to have comparable cardiovascular effects in PAH patients, but probably less side effects than 40 mg Tadalafil. Therefore, in our study Tadalafil 20 mg OD will be compared to placebo.

3.3 Explanation for choice of placebo

At present, no drug has shown in randomized clinical trials to prevent progressive RV failure in adults with a systemic RV. Therefore, Tadalafil will be compared against placebo.

3.4 Risks / benefits

Adults with a systemic RV are a remarkable group of patients. Most of them are survivors of a surgical procedure (i.e. atrial switch procedure for complete TGA) that is no longer performed. D-TGA is one of the most common cyanotic heart defects in the neonatal period.[14] Before the atrial switch operation was invented in the late 1950s, all of these patients died in the neonatal period. After the introduction of the atrial switch operation, the majority of patients survived into adulthood. Although the atrial switch operation was superseded by the arterial switch operation in the 1990s, the majority of patients who underwent an atrial switch procedure is still alive and are now young or middle-aged adults. These patients are risk of developing end-stage HF and premature death. Recognizing both their remarkable survivorship and ongoing risk, adults with a systemic RV merit focused scientific consideration despite low numbers. Currently, therapeutic recommendations in these patients are based on expert opinion and not on scientific evidence, with heart transplantation being the only option for end-stage HF patients.

Finally, one can argue that not only patients with a systemic RV might potentially benefit from this study, but all patients with end-stage HF waiting on the heart transplantation list for a new organ. Given the ubiquitous shortage of organ donors, medical options to improve the fate of a systemic RV will also be beneficial for non-CHD patients with end-stage HF, as the competition among transplant candidates for a limited number of organs might be tempered.

4. STUDY OBJECTIVES

4.1 Overall objective

The aim of the present study is to assess in a double-blind, randomized, placebo-controlled pilot trial the effect of PDE-5 inhibition with Tadalafil on RV size and function, exercise capacity and neurohumoral activation in adults with a systemic RV over a 3-year follow-up.

4.2 Primary objective

The primary objective of this study is to assess the improvement of Tadalafil on systemic RV endsystolic volume (ESV) measured by cardiovascular magnetic resonance imaging (CMR) or cardiac multirow detector computed tomography (CMDCT) - in patients with contraindications for cardiac MRI - at 3 years of follow-up.

4.3 Secondary objectives

The secondary objective of this study is to assess the effects of Tadalafil on systemic RV ejection fraction (EF) measured by CMR or CMDCT at 3 years of follow-up.

Another secondary objective of this study is to assess the effects of PDE-5 inhibition on exercise capacity and on serum neurohormonal activation in these patients at 3 years of follow-up.

4.4 Safety objectives

The study aims to assess long-term safety of Tadalafil and its tolerability in terms of incidence of the following Adverse Events (AE):

- Headache (reported > 10%)
- Epipharyngitis (reported > 10%)
- Nausea and dyspepsia (reported > 10%)
- Symptomatic arterial hypotension (reported 1-10%)

Some AE might trigger a drug dose change (see 8.3). As a safety objective, we want to achieve a study discontinuation rate due to AE lower than 20%. This figure appears to be a reasonable threshold for this potential new therapy. In the landmark trial investigating the role of Tadalafil in PAH, the discontinuation rate in the placebo group was 16% (13/82) and 11% (34/323) in the Tadalafil group.[41] We expect to observe similar or lower discontinuation rates in our patients, as they are less sick than patients with advanced PAH.

5. STUDY OUTCOMES

5.1 Primary outcome

Primary endpoint: Change in mean systemic RV ESV from baseline to study end at 3 years of follow-up, measured by CMR or CMDCT in patients with contraindications for CMR. In patients who have to discontinue the study medication prematurely, RV ESV will be measured again within 4 weeks of the study drug withdrawal, unless the treatment period was < 3 months. In patients not willing to undergo a CMR / CMDCT study at the time of premature study termination, the CMR / CMDCT data from 1 year's follow-up will be analyzed, if available.

Clinical relevance of primary endpoint: Left ventricular dimensions (end-systolic and end-diastolic volumes) and EF have been shown to be one of the most powerful predictors of survival in chronic left ventricular heart failure.[42] Dimensions and EF of the systemic ventricle (RV) are also important prognostic factors in adults with a systemic RV, and deteriorate over time.[8, 12, 13] We elected to use changes in RV ESV as primary endpoint for our trial for the following reasons:

- In patients with LV systolic dysfunction, short-term trial-level therapeutic effects of a drug or device on LV dimensions are associated with longer-term trial-level effects on mortality.[43, 44] We assume that the same prognostic assumptions between systemic ventricular volumes and hard clinical endpoints can be made for a failing RV: in a recent MRI based study with PAH patients and RV failure, RV ESV (but not end-diastolic volumes) at baseline were predictive of late RV failure leading to death or lung transplantation after a follow-up of 8 years.[45]
- MRI-based measurements of volumes have the highest reproducibility among all RV measures.[46]
- Measurement of RV ESV is likely more sensitive to detect changes in RV function in TGA patients than RV EF because:
  1) in patients with PAH, the RV adapts to its chronically increased afterload first by myocardial remodeling with hypertrophy and increased contractility.[47] If these compensatory mechanisms fail, the RV begins to dilate, followed by a decrease in RVEF. Accordingly, an increase in RV volumes precedes the decrease in RV EF. The systemic RV in patients with TGA may behave similarly.
  2) With progressive RV failure and RV dilatation, there is also an increase in secondary tricuspid regurgitation.[6] The increased amount of tricuspid regurgitation may falsely improve RV EF, whereas RV ESV will nevertheless be increased as sign of progressive RV failure.
- Performing a placebo-controlled trial that assesses differences in mortality is not feasible in TGA patients, as it would need to involve too large patient numbers.

5.2 Secondary outcomes

Secondary endpoints:

- Change in mean systemic RV EF from baseline to study end at 3 years of follow-up, measured by CMR or CMDCT in patients with contraindications for CMR. In patients who have to discontinue the study medication prematurely, RV EF will be measured again within 4 weeks of the study drug withdrawal, unless the treatment period was < 3 months. In patients not willing to undergo a CMR / CMDCT study at the time of premature study termination, the CMR /CMDCT data from 1 year's follow-up will be analyzed, if available.
- Change in exercise capacity measured as peak VO_2 during cardiopulmonary exercise testing from baseline to study end after 3 years of follow-up.
- Change in serum neurohormonal activation (BNP, NT-pro BNP, hs-cTn, MR-proANP, MR-proADM, Copeptin and Pro-endothelin-1) from baseline to study end at 3 years of follow-up.

In patients who have to discontinue the study medication prematurely or decide to terminate the study prematurely, exercise capacity and neurohumoral activation will be re-measured within 4 weeks of the

study drug withdrawal, unless the treatment period was < 3 months.

5.3 Safety outcomes

The following AEs will be collected:

- headache
- deterioration in renal function defined as an increase of 50% in serum Creatinine on at least two measurements (at least 6 days apart), or a drop in GFR below 30ml/min on two measurements (at least 6 days apart)
- allergic reactions
- epipharyngitis
- nausea and dyspepsia
- symptomatic arterial hypotension

The occurrence of these AEs together with the study discontinuation rate due to AE will be part of the annual safety report (see 10.1.2).

The following SAEs will be collected:

- Hospitalization for heart failure
- Death

6. STUDY DESIGN

6.1 General study design and justification of design

This study will use a parallel group, double-blind, randomized, placebo-controlled, multi-center, superiority trial design. Patients meeting the inclusion and exclusion criteria will be allocated randomly to Tadalafil vs. Placebo treatment in a 1:1 ratio at the screening visit, using a web-based randomization system. Randomization will be stratified by center and pacemaker implant at screening. The effect of PDE-5 inhibition with Tadalafil on RV size and function, exercise capacity and neurohumoral activation in adults with a systemic RV will be assessed over a 3-year follow-up.

One may argue, that the primary endpoint should be measured earlier than 3 years, e.g. at 3-6 months, as the effects of Tadalafil on RV size and function are likely to be expressed before a 3 year follow-up period. However, currently not foreseeable confounders may attenuate the early beneficial effects of Tadalafil on RV function in the long term. Considering the rationale of our study (i.e. reducing the heart failure risk in TGA patients in the long run), a follow-up period of years is mandatory, independent of any early effects, to ensure that long term Tadalafil medication has truly beneficial effects in these patients.

6.2 Methods of minimising bias

The randomized allocation lists (Tadalafil vs Placebo in 1:1 ratio) will be generated by an independent statistician using a random seed, with the help of a computer program, and lists will be generated stratified according to site and presence of pacemaker at baseline (with randomly varying block sizes of 2, 4 or 6 patients). Lists will be deposited password protected in a dedicated folder on a central GCP-compliant server.

The randomized allocation lists will be implemented in the electronic data capturing system and are concealed from all study personnel. As soon as the patient fulfills the inclusion and exclusion criteria, the study personnel can select the randomize button and the patient will be randomized according to the concealed list, the list appropriate to the site and presence/absence of pacemaker at baseline.

The study personnel will randomize the patients.

All study personnel, including CMR or CMDCT assessors, trial statistician and central data monitors will remain blinded after the assignment of the treatments. Packages containing the drugs (Tadalafil pills or similarly looking Placebo pills) will only contain identifiers to allow emergency unblinding.

6.3 Unblinding procedure (Code break)

All serious adverse events (SAE) will be directly reported to the Sponsor / Coordinating Investigator and may trigger emergency unblinding by the DSMB if the SAE is unexpected and suspected to relate to the treatment (SUSAR, see 10.1.1).

In case of a medical reason for emergency unblinding, the pharmacy at the Bern University Hospital provides a 24/7 service with a pharmacist on call outside normal opening hours. The investigator will have first to contact the pharmacist on call and inform him/her about the need for unblinding. The requesting investigator will then have to send a specific unblinding form per fax (Number +41 31 632 47 90) to activate the procedure. The pharmacist has access to the randomization list linking the patient's study number with the randomly allocated treatment.

7. STUDY POPULATION

Currently, based on the data of the Swiss Registry for Adults with Congenital Heart Disease, there are an estimated 300-600 adults living in Switzerland with a RV in subaortic (systemic) position. Many of these patients are followed at the following regional or supraregional centers for adults with congenital heart disease:

- University Hospital Basel
- University Hospital Bern (Inselspital)
- University Hospital Geneva (HUG)
- University Hospital Lausanne (CHUV)
- University Hospital Zurich (USZ)
- Kantonsspital St. Gallen

All these centers are participating in this trial. The heads of the centers are represented as Co-applicants or Partners of this study proposal. In addition, all members of the WATCH, including members not working at one of the centers, will be informed about this trial and asked to refer patients to one of the recruiting centers.

In addition to Swiss patients, adults with a systemic RV and regular follow-up at the University Hospital Vienna have also the possibility to participate at this trial. This will further increase the eligible patient number by n=100.

All eligible patients will be informed about the study and asked for consent during the regular clinical visits.

7.1 Eligibility criteria

Inclusion criteria:

- Adults (≥18 years) with a systemic RV due to due to D-TGA repaired with an atrial switch procedure or due to ccTGA

Exclusion criteria:

- Incapability of giving informed consent
- Myocardial infarction, stroke, or open heart surgery within the 3 months prior to baseline visit
- Expected heart transplant within the next 6 months starting from baseline
- Pregnant or nursing women (a pregnancy test is mandatory prior to randomization; women of childbearing potential must agree to use reliable contraception from randomization to end of study treatment)
- Severe renal insufficiency (Creatinine clearance ≤ 30 ml/min)
- Severe hepatic insufficiency (Child-Pugh-Class C)
- Hypotension with blood pressures < 90/50 mmHg at the baseline visit
- Hypersensibility to Tadalafil
- Allergy to iodinated (in patients undergoing CMDCT) or Gadolinium-based (in patients undergoing CMR) contrast agents.
- Co-medication with nitrates
- Regular use of “poppers”, i.e. alkyl nitrites, that are inhaled for recreational purposes, including as club drugs used at dance clubs.
- Co-medication with potent CYP3A4 inhibitors: Ketoconazol, Ritonavir, Rifampicin
- Co-medication with other PDE-5 inhibitors for erectile dysfunction during the last four weeks prior to baseline visit
- Medical history of Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)
- Hereditary Galactose intolerance, Lactase deficiency or Glucose-Galactose-Malabsorption
- Participation at another clinical trial in which the primary endpoint has not been reached.

Remark: Male patients taking PDE-5 inhibitors for erectile dysfunction can be included in this trial if

they agree to discontinue their usual medication for erectile dysfunction permanently at least 4 weeks prior to baseline visit.

7.2 Criteria for withdrawal / discontinuation of participants

Patients can withdraw their consent without reason at any time. In such a case, the study medication will be immediately stopped. At the time the study medication is stopped, the exams as scheduled at the study end will be repeated, unless the study entry was less than 3 months before or the patient has withdrawn his/her consent for any further exams.

No change in study medication during the trial is possible on request, except if medically indicated, see 8.3.

8. STUDY INTERVENTION

8.1 Identity of investigational treatment

Experimental Group: Tadalafil 20 mg p.o. once per day (OD) for 3 years

Control Group: placebo p.o. OD for 3 years.

The study medication (verum and placebo) will be provided by the pharmacy of the University Hospital Bern.

All participants will be started on Tadalafil 20 mg or placebo OD without any titration period.

The investigational medicinal product (IMP; both verum and placebo) will be specifically labeled according to GMP by the pharmacy of the Inselspital.

The IMP will be stored in a secure, limited access storage area under the recommended storage conditions in a locked area with temperature control.

8.2 Administration of experimental and control interventions

At present, no drug has shown in randomized clinical trials to prevent RV failure in adults with a systemic RV. Therefore, Tadalafil will be compared against placebo.

8.3 Dose modifications

Drug dose changes in response to harm:

- Headache: In a first step, Paracetamol p.o. will be prescribed up to 1g ter in die (TID) to relief headaches; in case of an insufficient response, temporarily lowering of the study drug to 10 mg OD for 4 weeks will be allowed. In case of recurrence of headaches after increasing the study drug to 20 mg OD after 4 weeks, the study drug will be lowered permanently to 10 mg OD. If this dosage is also not tolerated in the long term, the trial medication will be permanently withdrawn. In patients who have to discontinue the study medication prematurely, the primary and secondary endpoints will be re-measured within 4 weeks of the study drug withdrawal, unless the treatment period was < 3 months or the patient refuses further exams. The permanent discontinuation of the study drug will be reported as an AE.

- Renal function impairment: Since Tadalafil is excreted by the kidney, its use is contra-indicated in patients with severe renal impairment (Creatinine clearance ≤ 30 ml/min). If renal function deteriorates to this extent during the study period, the trial medication will be permanently withdrawn from the patient. In patients who have to discontinue the study medication prematurely, the primary and secondary endpoints will be re-measured within 4 weeks of the study drug withdrawal, unless the treatment period was < 3 months or the patient refuses further exams. The permanent discontinuation of the study drug will be reported as an AE . In patients with moderate or mild renal impairment (Creatinine clearance > 30 ml/min), serum Creatinine will be monitored yearly during therapy or more frequently if clinically necessary.

- Allergic Reactions: Allergic skin reactions have been observed in rare cases. If this is suspected, the trial medication will be permanently withdrawn from the patient. In patients who have to discontinue the study medication prematurely, the primary and secondary endpoints will be re-measured within 4 weeks of the study drug withdrawal, unless the treatment period was < 3 months or the patient refuses further exams. The permanent discontinuation of the study drug will be reported as an AE .

Drug dose changes in response to new co-medication during the study period:

- potent CYP3A4 inhibitors: If co-medication with Ketoconazol, Ritonavir or Rifampicin will be become clinically indicated during the study period, the trial medication will be interrupted during this time.
- PDE-5 inhibitors: If co-medication with PDE-5 inhibitors becomes clinically indicated during the study period (i.e. for erectile dysfunction), the trial medication will be interrupted during this time.

Improving/worsening disease:

- Any changes in cardiac medication are allowed, with the exception of Nitrates. If co-medication with Nitrates will become clinically indicated during the study period, the trial medication will be interrupted during this time.

8.4 Compliance with study intervention

Randomized and blinded packages of the study drug or placebo will be dispensed to the patients on a regular basis and empty packages will be sent to the sites or, alternatively, the patient can bring the empty packages and give it to the study nurse during a clinical visit. Drug use will be entered into the database and the study personnel will discuss with the patients during intermediate phone calls and during the clinical visits when the patient had an adherence of less than 90% to understand the reasons for their limited adherence (see 7.2 and 8.3).

8.5 Data Collection and follow-up for withdrawn participants

Patients can withdraw their consent without reason at any time. In such a case, the study medication will be immediately stopped. At the time the study medication is stopped, the exams as scheduled at the study end will be repeated, unless the study entry was less than 3 months before or the patient has withdrawn his/her consent for any further exams.

If the consent is revoked, the data collected up to the time of withdrawal will be used until final completion of the data analysis and anonymized afterwards.

8.6 Concomitant treatments

All concomitant cardiac care and interventions are permitted during the study period, with the exception of nitrates. As none of the current drugs used for left heart failure have shown to improve outcome in patients with a systemic right ventricle, no restrictions regarding the use of beta-blockers or other heart failure regimens are necessary.

8.7 Study drug accountability

The pharmacy of the Inselspital will establish and maintain adequate records from shipment to the sites until return or disposal including the physical location, dates (receipt, expiry, use, return), lot/batch number and quantities (received, used, destroyed).

Sites will be responsible for local accountability and its proper documentation of the IMP, from the reception, distribution to the patient, returns from the patient to the destruction of the remaining lock stock if any.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

Visit	**BL***	**Visit 1**	**PC1****	**PC2****	**PC3****	**Visit 2**	**PC4****	**Visit 3**	**PC5****	**Visit 4**	**PC 6 Safety FU**
Time (months)	0	1	3	6	9	12	18	24	30	36	37
Window (weeks)	0	+ 2	+2	+2	+2	+ 4	+2	+ 4	+2	+ 4	± 1
Informed Consent	X										
Eligibility criteria	X										
Demography	X										
Medical history	X										
QoL	X					X				X	
Randomization	X										
Clinical examination	X	X				X		X		X	
IMP delivery	X					X		X			
IMP accountability		X				X		X		X	
ECG	(X)	X				(X)		(X)		(X)	
Holter	(X)									(X)	
CMR / CMDCT	X					X				X	
CPET	X									(X)	
Blood analysis	(X)	X				(X)		(X)		(X)	
Neurohormones	X					X				X	
TTE	(X)					(X)		(X)		(X)	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	
Adherence			X	X	X		X		X		
AE/SAE		X	X	X	X	X	X	X	X	X	X

(X) Not study specific, only collected if performed per routine

* Baseline (BL) exams

**Phone call (PC) to control adherence to IMP

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

CMR will be performed in all patients at baseline, at 1 year and at 3-year follow-up. Image acquisition will be performed with a 1.5-T scanner using a standardized protocol to diminish inter-observer variability between the different centers. A position paper of a group of Swiss pediatric and adult cardiologists and radiologists performing CMR in congenital heart disease has been published, endorsed by the working groups “Adult Congenital Heart Disease” and “Echocardiography and Cardiac Imaging” of the Swiss Society of Cardiology, the Swiss Society of Pediatric Cardiology and the “Ressort Cardiac Imaging” of the Swiss Society of Radiology. The recommendations for imaging a systemic RV as outlined in this paper will be followed for this trial.[48] According to this protocol, the CMR study will assess systemic and pulmonary venous return by contrast-enhanced MR angiography and exclude shunting by flow measurements in the aorta and both pulmonary arteries.

CMDCT will be performed in patients with contraindication for cardiac MRI at baseline, at 1 year and at 3-year follow-up to establish the primary endpoint. Images will be obtained by contrast-enhanced, electrocardiogram (ECG) gated cardiac MDCT in cranio-caudal direction during inspiratory breath hold. Axial images of 10 cardiac phases are acquired in steps of 10% of the R-R interval. To depict the whole heart, 60-80 slices are made each with 2 mm thickness and no interslice gap. From these, 12-15 short-axis reconstructions will be created for functional analysis.

Cardiac MRI and CMDCT image analysis: Cine loops will be used to define end diastole (largest RV volume) and end systole (smallest RV volume). Trabeculations and papillary muscles will be considered part of the ventricular cavity. The sums of traced contours in end diastole and end systole will be used to calculate end-diastolic and end-systolic volumes using a disc summation method.[48]

To minimize bias image analysis, measurement of ventricular volumes will be performed in core labs by experienced cardiologists or radiologists with training in CMR or CMDCT. CMR and CMDCT data will be analysed by different core labs. The encoded images will be sent electronically to the coordinating investigator responsible for the CMR or CMDCT core lab. To decrease the variability in RV ESV, every measurement will be performed twice, by 2 different readers, and the mean volume will be used for study purposes.

Furthermore, the core lab will establish and assess any parameters derivable from the existing image datasets that might be relevant for the study.

9.2.2 Assessment of secondary outcomes

RV EF will be measured according to the same principles as outlined above for the primary endpoint.

Cardiopulmonary exercise testing (CPET) will be performed in all patients at baseline and at study end. Before exercise, respiratory flow loops will be acquired and maximal breathing capacity determined. Patients will be placed on a cycle ergometer to perform continuous measurements of minute ventilation, oxygen consumption, carbon dioxide production, heart rate, blood pressure and electrocardiography. Workload will be increased by 5 to 15 Watts in a stepwise manner, depending on the individually predicted maximum exercise capacity, in such a way that maximal possible effort can be attaint in 10-15 minutes. Peak VO_2 is defined as the highest value of oxygen consumption during the last 30 s of peak exercise. A 12-lead ECG will be continuously recorded and a finger pulse oximeter is used for continuous measurement of arterial oxygen saturation. The following additional parameters will be assessed: VE/VCO_2 Slope, $PETCO_2$, O_2 pulse trajectory, delta VO_2/delta W trajectory, heart rate kinetics and heart rate recovery (HRR). Measurements and reporting of these data follow the recommendations of the European Association for Cardiovascular Prevention and Rehabilitation.[49]

To minimize bias in data analysis, measurement of the secondary endpoint will be performed in a core lab by experienced cardiologists with training in cardiopulmonary exercise testing. The encoded data recorded during the CPET studies will be sent electronically to the coordinating investigator

responsible for the CPET core lab.

Neurohumoral activation will be measured in all patients at baseline, at 1 year and at study end. Concentrations of the neurohormones B-type natriuretic peptides (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitive cardiac troponin (hs-cTn), A-type natriuretic peptide (MR-proANP), Pro-adrenomedullin, Copeptin and Pro-endothelin-1 will be measured at a single core-lab with expertise in biomarkers (Cardiovascular Research Institute Basel, CRIB).

Specific patients sets with plastic tubes and barcodes corresponding to the individual patient numbers and time points in the study will be used. Samples will be collected locally, followed by centrifugation, aliquoting and initial storage at -80 degrees at very center. Regular pick up of samples at the individual hospitals and transport to the dedicated biobank at the CRIB will be provided by the core-lab. The blood samples will be stored in Basel for 10 years. Biomarkers will be measured in 2 batches from the frozen samples. If within the time period of 10 years new biomarkers for quantifying neurohumoral activation emerge, the stored blood samples may be re-analyzed with these new biomarkers.

9.3 Procedures at each visit

Baseline Visit:

- Clinical examination†*
- Assessment of quality of life by a linear analog scale (LAS), the Satisfaction with Life Scale (SWLS)[50] and the General Self-Efficacy (GSE) Score.
- 12-channel ECG†*
- Holter-ECG for 24 hours†*
- Transthoracic echocardiography†*
- CPET**
- CMR** or CMDCT in patients with contraindications for CMR
- Routine bloodwork†*: routine hematology block, INR, chemistry (Na, K, Creatinine, Urea)
- Neurohormones

Visit 1, 4 week follow-up:

- Clinical examination
- 12-channel ECG
- Routine bloodwork
- IMP accountability
- Assessment of concomitant medication, AE/SAE

Visit 2, 1 year follow-up:

- Clinical examination†*
- Assessment of quality of life by LAS, SWLS and GSE-Score.
- 12-channel ECG†*
- Transthoracic echocardiography†*
- CMR** or CMDCT in patients with contraindications for CMR
- Routine bloodwork†*: routine hematology block, INR, chemistry (Na, K, Creatinine, Urea)
- Neurohormones
- IMP accountability
- IMP delivery
- Assessment of concomitant medication, AE/SAE

Visit 3, 2 years follow-up:

- Clinical examination†*
- 12-channel ECG†*
- Transthoracic echocardiography†*
- Routine bloodwork†*: routine hematology block, INR, chemistry (Na, K, Creatinine, Urea)
- IMP accountability
- IMP delivery
- Assessment of concomitant medication, AE/SAE

Visit 4, 3 years follow-up:

- Clinical examination†*
- Assessment of quality of life by LAS, SWLS and GSE-Score
- 12-channel ECG†*
- Holter-ECG for 24 hours†*
- Transthoracic echocardiography†*
- CPET**
- CMR or CMDCT in patients with contraindications for CMR
- Routine bloodwork†*: routine hematology block, INR, chemistry (Na, K, Creatinine, Urea)
- Neurohormones
- IMP accountability
- Assessment of concomitant medication, AE/SAE

Phone calls after 3, 6, 9, 18 and 30 months

- Verification of adherence to IMP
- Collection of concomitant medication
- Collection of AE/SAE

Safety Follow-up (by telephone):

- Assessment of AE / SAE

† not study specific data, will only be collected if performed per routine

* these exams are routinely performed on an annual base in patients with a systemic right ventricle, ** or every 3 years.[51]

Transthoracic echocardiograms will be acquired following a detailed pre-specified protocol. For the purpose of data analysis, all echocardiograms will be analyzed in a central echocardiography core-lab. Studies will be sent to the core-lab in DICOM-format. For offline analysis of myocardial deformation (strain analysis) Tom-Tec-software will be used, which is vendor-independent.

In case of consent withdrawal from a patient, the study medication will be stopped immediately. The exams as scheduled at the study end will be repeated within 4 weeks of the study medication withdrawal, unless the study entry was less than 3 months before or the patient has withdrawn its consent for any further exams.

10. SAFETY

During the entire duration of the study, specific adverse events (AE) (see 5.3) and all serious adverse events (SAEs) will be collected, fully investigated and documented in source documents and case report forms (CRF). Study duration encompasses the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including a safety follow-up period of 1 month after the last visit (36 month Follow-up visit)..

10.1 Safety reporting

10.1.1 Definition and assessment of (serious) adverse events and other safety related events

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2]

A Serious Adverse Event (SAE) is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

As part of the study protocol, the following SAE will be collected and reported to the DSMB:

- Death from any cause
- Hospitalization for heart failure

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

SAEs will be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination (including the safety follow-up period of 1 month) will be further followed up until recovery or until stabilisation of the disease after termination.

<u>Assessment of Causality</u>

Both Investigator and Sponsor / Coordinating Investigator make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after de-challenge* Recurrence after re-challenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after de-challenge No other cause evident
Possibly	Temporal relationship

	Other cause possible
Unlikely	Any assessable reaction that does not fulfill the above conditions
Not related	Causal relationship can be ruled out
*Improvement after de-challenge only taken into consideration, if applicable to reaction	

Unexpected Adverse Drug Reaction

An “unexpected” adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator’s Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively). [ICH E2A]

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The DSMB will evaluate any SAE that has been reported regarding seriousness, causality and expectedness. If the event is categorized as “possibly”, “probably” or “definitively” related to the investigational product and is both serious and unexpected, it will be classified as a potential SUSAR. A potential SUSAR will require unblinding to determine a SUSAR. The DSMB will provide an overall assessment of benefit and harm given the observed rates of SAE at that time.

10.1.2 Reporting of serious adverse events (SAE) and other safety related events

Reporting of SAEs

All SAEs must be reported immediately and within a maximum of 24 hours of awareness to the Sponsor / Coordinating Investigator of the study. The Sponsor / Coordinating Investigator will re-evaluate the SAE and return the form to the site.

SAEs resulting in death are reported to the CEC and (if applicable) to the responsible local Ethics Committee (via the Sponsor / Coordinating Investigator) within 7 days.

Reporting of SUSARs

A SUSAR needs to be reported to the CEC and (if applicable) to the responsible local Ethics Committee and to Swissmedic (via Sponsor / Coordinating Investigator) within 7 days, if the event is fatal, or within 15 days (all other events).

The Sponsor / Coordinating Investigator must inform all Investigators participating in the clinical study of the occurrence of a SUSAR.

Reporting of Safety Signals

All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e. so called safety signals, must be reported to the Sponsor / Coordinating Investigator within 24 hours. The Sponsor / Coordinating Investigator must report the safety signals within 7 days to the CEC and (if applicable) to the responsible local Ethics Committee and to Swissmedic.

The Sponsor / Coordinating Investigator must immediately inform all participating Investigators about all safety signals.

Reporting and Handling of Pregnancies

Pregnant participants must immediately be withdrawn from the clinical study. Any pregnancy during the treatment phase of the study and within 30 days after discontinuation of study medication will be reported to the Sponsor / Coordinating Investigator within 24 hours. The course and outcome of the

pregnancy should be followed up carefully, and any abnormal outcome regarding the mother or the child should be documented and reported.

Periodic reporting of safety

An annual safety report is submitted once a year to all Ethics Committees and to Swissmedic via Sponsor/Coordinating Investigator. The annual safety report will contain information from all sites. The Sponsor/Coordinating Investigator will prepare the report.

11. STATISTICAL METHODS

11.1 Hypothesis

All primary and secondary endpoints will be analysed by intention-to-treat, tested using two-sided superiority testing with alpha set at 5% (0.05).

The primary hypothesis tested is that patients randomized to treatment with Tadalafil will improve systemic RV ESV compared to the patients randomized to treatment with Placebo. RV ESV will be measured by CMR or CMDCT. In patients who have to discontinue the study medication prematurely, the RV ESV will be re-measured within 4 weeks of the study drug withdrawal and this measurement will then be used for the primary endpoint analyses, unless the treatment period was < 3 months. The difference in RV ESV between baseline and the last CMR /CMDCT measurement will serve as primary endpoint.

Secondary endpoints are change in RV EF measured by CMR or CMDCT, change in exercise capacity measured as peak VO2 during cardiopulmonary exercise testing and change in serum neurohormonal activation (seven biomarkers: BNP, NT-pro BNP, hs-cTn, MR-proANP, Pro-adrenomedullin, Copeptin and Pro-endothelin-1) from baseline to study end at 3 years of follow-up or at the time of permanent discontinuation of the randomized treatment if stopped before 3 years of follow-up. Again, in patients who have to discontinue the study medication prematurely, RVEF, exercise capacity and neurohumoral activation will be re-measured within 4 weeks of the study drug withdrawal, unless the treatment period was < 3 months.

11.2 Determination of sample size

The sample size calculation is based on the primary endpoint - the change in RV ESV. In a representative sample of n=79 TGA patients with a systemic RV from Bern and Zurich with CMR data, the RV end-systolic volume was 122±34 ml.[52] Assuming that RV ESV improve or remain stable in the Tadalafil group and increase by 20% in the Placebo group to 146±39 ml, 78 patients are required to obtain an 80% power to detect this difference in RV end-systolic volumes between the 2 treatment groups with a two-sided alpha set at 0.05. Considering a possible dropout of 20%, 98 patients will be required (49 patients for each group). Assuming that not all right ventricles may respond similarly to Tadalafil, we elected to account for this phenomenon by increasing the standard deviation in the follow-up exam from 34 ml to 39 ml.

For comparison, in the previously mentioned PAH study investigating the prognostic values of RV volumes on long-term outcome, mean RV ESV at baseline were 90±22 ml in long-term stable patients and 118±24 ml in patients with progressive RV failure at long-term.[45]

This sample size will also allow detecting a 5% difference in EF between the 2 treatment groups, assuming a standard deviation in RV EF of 8%.

The following number of patients are expected to be recruited at each site (n): University Hospital Basel (n=5), University Hospital Bern (Inselspital, n=23), University Hospital Geneva (HUG, n=5), University Hospital Lausanne (CHUV, n=12), University Hospital Zurich (USZ, n=23), Kantonsspital St. Gallen (n=5), University Hospital Vienna (n=23).

11.3 Statistical criteria of termination of trial

As no interim analysis is planned, no statistical criteria have been defined for early termination of the trial.

Early termination of this trial is considered in case of insufficient recruitment (< 80 patients in the first year) or if safety issues arise (SAE's / SUSAR's).

11.4 Planned analyses

A detailed statistical analysis plan (SAP) will be written as a separate document. All analyses will be performed by the trial statistician, who will remain blind to the actual randomized treatment allocation, after completion of the data capture after 3 years of follow-up.

11.4.1 Datasets to be analysed, analysis populations

The full-analysis population consists of all patients randomized. The primary and secondary endpoints of patients randomized to Tadalafil will be compared to the patients randomized to Placebo by the intention-to-treat principle.

The safety population consist of all patients randomized, which received at least one dose of the randomized drug (Tadalafil or Placebo), and the patient's time at risk for safety endpoints are censored at the termination of the randomized drug intake.

11.4.2 Primary analysis

The primary endpoint will be analysed using ANCOVA (Analysis of Covariance), with RV ESV (in ml) at 3 years (or earlier if drug withdrawal) as the response variable, randomized treatment as main independent variable, baseline RV ESV (ml) and time between baseline and follow-up RV volume measurement (in months since baseline) as covariates.

11.4.3 Secondary analyses

Secondary endpoints will be analysed using ANCOVA (Analysis of Covariance) or Tobit regression or Multiple Imputation ANCOVA (see below), with the secondary endpoint (RV EF, peak VO2, BNP, NT-pro BNP, hs-cTn, MR-proANP, Pro-adrenomedullin, Copeptin or Pro-endothelin-1) at 3 years (or earlier if drug withdrawal) as the response variable, randomized treatment as main variable, baseline measurement (RV EF, peak VO2, BNP, NT-pro BNP, hs-cTn, MR-proANP, Pro-adrenomedullin, Copeptin or Pro-endothelin-1; respectively) and time between baseline and follow-up measurement time (in months since baseline) as covariates.

The seven biomarkers will be evaluated for the presence of values below the lower detection threshold, and for values above the upper detection threshold. If no values are recorded below the lower or above the upper detection threshold, ordinary ANCOVA will be used (as described above). If less then 30% of the values are recorded below the lower or above the upper detection threshold at follow-up, Tobit regression will be used (i.e. model with left and/or right censoring at the detection thresholds). If more than 30% of the values are recorded below the lower or above the upper detection threshold at follow-up, or if any baseline value is recorded below the lower or above the upper detection threshold, follow-up values and baseline values fulfilling these criteria will be multiple imputed using chained equations (see SAP, i.e. to impute in the range below or above the thresholds, as appropriate) and accordingly 20 data-sets will be created. The effect estimates will be estimated using ANCOVA with the respective biomarker at follow-up as response (BNP, NT-pro BNP, hs-cTn, MR-proANP, Pro-adrenomedullin, Copeptin or Pro-endothelin-1), baseline measurement of the respective biomarker and follow-up measurement time (in months since baseline) as covariate for each of the 20 imputed data-sets, and the estimates will be combined into one estimate and p-value using Rubin's rule.

11.4.4 Interim analyses

No interim analyses are planned.

11.4.5 Safety analysis

Safety endpoints will be analysed in the Full-analysis population and again separate also for the Safety population (Appendix of the main manuscript).

Safety endpoints are the following events: headache, renal function impairment, allergic reactions, epipharyngitis, nausea and dyspepsia, symptomatic arterial hypotension.

In the Full-analysis population, safety endpoints will be compared as number of events per patient in the ones randomized to Tadalafil vs. number of events per patient in the ones randomized to Placebo, using Poisson regression with time to last assessment as offset (i.e. days between baseline and 3 years follow-up or discontinuation of the drugs).

In the Safety-analysis population, safety endpoints will be compared as number of events per patient in the ones randomized to Tadalafil vs. number of events per patient in the ones randomized to Placebo, using Poisson regression with time to last assessment as offset (i.e. days between baseline and 3 years follow-up or discontinuation of the drugs, censoring at time of randomized drug withdrawal.

11.4.6 Deviation(s) from the original statistical plan

Deviations from the original SAP are not intended and will be reported in amendments of the SAP.

If potential new biomarkers - beyond the seven biomarkers reported above - become available during the conduct of the trial, and if these biomarkers will also be evaluated as secondary endpoints, these new biomarkers will be analysed using the same methodology as specified above for the seven pre-defined biomarkers..

11.5 Handling of missing data and drop-outs

A sensitivity analysis will be done on all primary and secondary endpoints using multiple imputation to account for missing baseline measurements (i.e. covariates used) and follow-up information (i.e. change from baseline), see SAP.

12. QUALITY ASSURANCE AND CONTROL

The Sponsor / Coordinating Investigator will ensure proper initial training of participating sites. The local investigator is responsible to provide adequate training all involved study personnel. Local investigators are required to maintain on file in an appropriate Investigator Site File the following accurate, complete and current records relating to this study:

- all documents, correspondence and approvals relating to the study (essential documents according to ICH GCP Chapter 8).
- all clinical forms and documentation (see 12.1).

12.1 Data handling and record keeping / archiving

The Local Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation.

12.1.1 Case Report Forms

An electronic data capture (EDC) system will be built for the study using the SecuTrial platform. The EDC system will include electronic case report forms (eCRFs) designed to capture study information, which are completed by trained site staff. eCRFs documenting SAEs will have to be submitted via the EDC system within 24 hours after the investigator becomes aware of the event. All other eCRFs should be completed in a timely manner, preferably within 5-10 days of the subject's enrollment or follow-up visit. All data collected will not be identifiable reference to the subjects. The subject's anonymity will be maintained and the confidentiality of records and documents that could identify subjects will be protected, respecting the privacy of and confidentiality rules in accordance with applicable regulatory requirements.

Subjects will be identified only by their assigned study number and initial on all CRFs and other records and documents submitted to the investigators, the monitor, and other authorised parties.

The investigator will keep a Patient Identification List with complete identification information (name, address, contact number) on each subject.

The investigator will maintain all study documents in strict confidence.

CRF entries will be performed by authorized persons and it will be assured that any authorized person can be identified.

12.1.2 Specification of source documents

Source data must be available at the site to document the existence of the study participants. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant. Source documents include demographic data, visit dates, participation in study and Informed Consent Forms, randomisation number, IMP patient accountability log, SAEs and concomitant medication and results of relevant examinations. Each follow-up visit will be reported in the source data and should at least contain the information required according the protocol. The investigator assures that source documents are appropriately stored and completed. The investigator assures that medical files and CRFs are accessible for inspection by authorities and monitoring visits

12.1.3 Record keeping / archiving

All study data must be archived for a minimum of 10 years after study termination or premature

termination of the clinical trial.

12.2 Data management

12.2.1 Data Management System

The CRFs in this trial are implemented electronically using a dedicated electronic data capturing (EDC) system (secuTrial®). The EDC system is activated for the trial only after successfully passing a formal test procedure. All data entered in the CRFs are stored on a Linux server in a dedicated Oracle database.

Responsibility for hosting the EDC system and the database lies with Inselspital Bern.

12.2.2 Data security, access and back-up

The server hosting the EDC system and the database is kept in a locked server-room. Only the system administrators have direct access to the server. A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission for each user to use the system and database as he/she requires.

All data entered into the CRFs are transferred to the database using Secure Sockets Layer (SSL) encryption. Each data point has attributes attached to it identifying the user who entered it with the exact time and date. Retrospective alterations of data in the database are recorded in an audit table. Time, table, data field and altered value, and the person are recorded (audit trail). A multi-level back-up system is implemented.

12.2.3 Analysis and archiving

At final analyses, data files will be extracted from the database into statistical packages to be analyzed. The status of the database at this time is recorded in special archive tables.

The study database with all archive tables will be securely stored by Inselspital Bern. The sponsor also keeps the Trial Master File and interim/final reports for at least 10 years.

12.2.4 Electronic and central data validation

Data is checked by the EDC system for completeness and plausibility. Furthermore, selected data points are cross-checked for plausibility with previously entered data for that participant. In addition (if applicable), central data reviews will be performed on a regular basis to ensure completeness of the data collected and accuracy of the primary outcome data.

12.3 Monitoring

Monitoring will verify that the rights and well-being of the patients are protected, the trial is conducted according to GCP and that the protocol is followed. A specific monitoring plan will be developed. The dates of the visits will be recorded by the monitor in a log kept at the site. The source data/documents should be accessible to monitors and questions should be answered during monitoring. The Local Investigator and their relevant personnel should be available during monitoring visit and possible audits and sufficient time should be devoted to the process. The progress of the study will be monitored by:

- Ensuring completed eCRFs match source documents, and resolution of any discrepancies. Direct access to complete source documents must be made available during monitoring visits for verification of eCRF data.

- Periodic on-site visits and, if necessary, remote monitoring of data.
- Frequent telephone or email communications between the investigator and assigned study site monitors.
- Appropriate computer edit programs will be run to verify the accuracy of the database.

12.4 Audits and inspections

The study site may be subject to audits and inspections to verify that the rights and well-being of the patients are protected, the trial is conducted according to GCP and that the protocol is followed. The study documentation and the source data/documents should be accessible to auditors/inspectors (also CEC) and questions should be answered during inspections. All involved parties must keep the participants identity data strictly confidential.

12.5 Confidentiality, data protection

Direct access to the source documents will be permitted for purposes of monitoring, audits and inspections (ICHE6, 6.10).

13. PUBLICATION AND DISSEMINATION POLICY

The wish of the steering committee is to make SERVE a project that

- has a high impact on clinical practice and research in Grown-Up Congenital Heart Disease (GUCH)
- allows to address different perspectives on patient outcomes in adults with a systemic right ventricle
- sets the signal for a good national collaboration among different specialists in the field of GUCH for the years to come

In order to optimize the potential of this project, a strategy for publications and authorship has been defined and distributed to all participating centers and core labs. Guidelines for authorship for the SERVE trial are based on published recommendations for authorship in multicenter studies.[53, 54] The present publication strategy follows the one used by Approach-IS Consortium.[55, 56]

All publications will follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors.

14. FUNDING AND SUPPORT

This trial is supported by a grant from the Swiss National Foundation for Research (SNF Project 33IC30_166855).

15. INSURANCE

Insurance will be provided by the Sponsor. A copy of the certificate is filed in each investigator site file and the trial master file.

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